SM

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/802,472	03/09/2001	Paz Einat	EINAT=4.1C	7736

1444 7590 07/22/2004

BROWDY AND NEIMARK, P.L.L.C.
624 NINTH STREET, NW
SUITE 300
WASHINGTON, DC 20001-5303

EXAMINER	
KIM, YOUNG J	

ART UNIT	PAPER NUMBER
1637	

DATE MAILED: 07/22/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/802,472	EINAT ET AL.	
	Examiner	Art Unit	
	Young J. Kim	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 July 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *9 and 13-17* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *9 and 13-17* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *26 June 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

This Office Action responds the Amendment received on July 6, 2004.

Based on a careful reconsideration of the application, the finality of the previous Office Action is hereby withdrawn.

Preliminary Remark

All rejections and objections hereto not reiterated are considered to be withdrawn.

In view of the papers filed July 6, 2004, it has been found that this nonprovisional application, as filed, through error and without deceptive intent, improperly set forth the inventorship, and accordingly, this application has been corrected in compliance with 37 CFR 1.48(a). The inventorship of this application has been changed by the addition of Aviv Regev as a co-inventor along with the previously named inventors, Paz Einat, Rami Skaliter, and Elena Feinstein.

The application will be forwarded to the Office of Initial Patent Examination (OIPE) for issuance of a corrected filing receipt, and correction of the file jacket and PTO PALM data to reflect the inventorship as corrected.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 9 and 13-15 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 13 and its dependent claims 9, 14 and 15 recite the limitation "the protein encoded by the DNA" in embodiment (a)(iii). There is insufficient antecedent basis for this limitation in the claim. A proper antecedent basis would be provided by amending the claim to recite the phrase, "the protein encoded by the full length cDNA."

Claims 14 and 15 recite the phrase, "polypeptide *in accordance* with claim 13," which renders the claim confusing. According to the definition set forth in Merriam-Webster's Online Dictionary (available through http://www.search.eb.com, attached hereto), the word, "accordance" has a definition of, "agreement," or "conformity." Based on this definition, the polypeptide of claims 14 and 15 becomes drawn to an isolated polypeptide "in agreement with," rendering the polypeptide confusing in what characteristic of the claimed polypeptide is in agreement with the polypeptide of claim 13. Using the common dependent claims language such as, "an isolated polypeptide of claim 13," would overcome this rejection.

Rejections – New Grounds

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 9 and 13-17 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Factors to be considered in determining whether a disclosure would require undue experimentation are summarized in In Re Wands (858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988)). They include (A) the quantity of experimentation necessary, (B) the amount of direction or guidance presented, (C) the presence or absence of working examples, (D) the nature of the invention, (E) the state of the prior art, (F) the relative skill of those in the art, (G) the predictability or unpredictability of the art, and (H) the breadth of the claims.

(A) Quantity of experimentation: the quantity of experimentation required to would be undue for the following reasons.

The specification discusses a cDNA microarray differential expression analysis conducted to identify genes that were responsive to hypoxia in human A172 glioma cells (page 111, [0272]), identifying mRNA of gene 95 as being significantly over-expressed under hypoxic conditions. The specification discloses that the over-expression was confirmed via Northern blot analysis (page 111, [0272]). The specification discloses that the human EST (expressed sequence tag) that contained a full-length cDNA was identified as the human 95 transcript (identified as SEQ ID NO: 3), wherein via *in vitro* translation of said cDNA, protein product of SEQ ID NO: 4 was identified.

While the specification discloses that the expression of mRNA (as represented by the polynucleotide of SEQ ID NO: 3) is elevated in cells treated with hypoxic conditions (pages 113-117), the specification is ***silent*** on whether the protein encoded by said mRNA is also elevated significantly or even expressed at all at a cellular level. The specification simply makes the correlation that because the mRNA is over-expressed, its encoded protein would be an excellent

candidate, "for diagnostic testing of tissue of fluid for having been subjected to hypoxia." (page 112, [0274, bottom].

As one skill in the art is aware, a single shift in the open reading frame of the nucleic acid coding sequence would generate an entirely different protein. Therefore, absent evidence that the protein of SEQ ID NO: 4 which is encoded by the polynucleotide of SEQ ID NO: 3 is actually present in cellular levels **and** that said protein is differentially (in this case, over-expressed) in cells subject to hypoxic conditions, one skilled in the art would not be able to practice the invention as claimed without undue experimentation.

Further, the claims are not only drawn to a polypeptide encoded by the full-length cDNA comprising a polynucleotide of SEQ ID NO: 3, but an isolated polypeptide comprising a protein encoded by **(a)** a naturally occurring polynucleotide having at least 70% identity with naturally occurring polynucleotide comprising SEQ ID NO: 3, **(b)** an isolated polypeptide comprising a protein encoded by a naturally occurring polynucleotide capable of hybridizing under moderately stringent conditions to a naturally-occurring polynucleotide of SEQ ID NO: 3 **(c)** or its 70% homologue, **(d)** a variant of an isolated polypeptide having at least 70% identity to the protein encoded by the polynucleotide of **(a), (b),** and **(c)**, or a functional derivative or salt of **(a), (b), (c), and (d)**; or a molecule which comprises the antigen-binding portion of an antibody specific for said isolated polypeptide.

Not only the specification lack evidence that the protein of SEQ ID NO: 4, encoded by the polynucleotide of SEQ ID NO: 3 is present at cellular level **and** over-expressed, but the specification further lacks evidence on whether the above recited sequence variants are present at the cellular level **and** whether they are over-expressed in cells subjected to hypoxic conditions.

Therefore, one skilled in the art would have to not only conduct experiment on the single disclosed polypeptide of SEQ ID NO: 3, but on all sequence variants of said polypeptide, none of which are disclosed as being over-expressed in cells subjected to hypoxic conditions, amounting to an undue amount of experimentation.

(B) Amount of Guidance/Direction: The specification provides evidence that the mRNA represented by the polynucleotide of SEQ ID NO: 3 is over-expressed in cells subject to hypoxic conditions (pages 111 and 113-117). The specification also discloses that the over-expression of said mRNA is observed in DNA damaging conditions, correlated with anti-proliferative activity (pages 113-114), correlated with apoptotic process (page 114-115). The specification, however, lacks any guidance in whether the protein of SEQ ID NO: 3, encoded by the polynucleotide of SEQ ID NO: 4 or any of the sequence variants recited above are similarly expressed. Additionally, claim 13, embodiment (c) is drawn to a "functional derivative," of the above polypeptide. However, the specification gives no disclosure or guidance on what the function of polypeptide of SEQ ID NO: 4 (encoded by the polynucleotide of SEQ ID NO: 3) is let alone the polypeptide sequence variants listed above.

(C) Absence of working examples: As already set forth, the specification provides working examples only for the polynucleotide of SEQ ID NO: 3, but not the polypeptide of SEQ ID NO: 4 or any of its sequence variants.

(D) The nature of invention: The nature of the invention relates to a protein, wherein its use is related to diagnostic marker of disease or medical condition.

(E) The state of prior art: The data in the specification show that gene copy number is increased in cells under hypoxic conditions. However, it does not necessarily follow that an

increase in gene copy number results in an increased protein expression, such that the antibodies would be useful diagnostically.

Haynes et al. (1998, Electrophoresis 19:1862-1871), who studied more than 80 proteins relatively homogeneous in half-life and expression level found no strong correlation between protein and transcript level. For some genes, equivalent mRNA levels translated into protein abundances which varied more than 50 fold. Haynes et al. concluded that the protein levels cannot be accurately predicted from the level of the corresponding mRNA transcript (pp. 1863, 2nd paragraph, and Figure 1).

Gygi et al. (Molecular and Cellular Biology, March 1999, vol. 19, no. 3, pages 1720-1730) who studied the correlation between the mRNA and protein expression levels for secreted genes concluded that the correlation between mRNA and protein levels was ***insufficient*** to predict protein expression levels from quantitative mRNA data (Abstract).

(F) Skill level: The skill level of the artisan is considered to be high.

(G) Unpredictability of the art: As already set forth above by Haynes et al. and Gygi et al., the art of correlating the protein expression level solely from quantitative mRNA data is unpredictable.

(H) Breadth of the claims: The breadth of the claims encompass a polypeptide encoded by a polynucleotide, wherein said polynucleotide is differentially expressed in cells subject to hypoxic conditions, but no evidence of likely expression at the protein level.

One skill in the art, would first look to the specification for example and guidance in determining whether the single disclosed species of polypeptide of SEQ ID NO: 4 is also over-expressed as its encoding polynucleotide of SEQ ID NO: 3, to which none would be found. One

skilled in the art, therefore, would be forced to look to the prior art which would indicate that correlating the protein expression levels solely based on mRNA expression analysis would be insufficient leading to an undue experimentation of a skilled artisan to use the polypeptide of SEQ ID NO: 4, encoded by the polynucleotide of SEQ ID NO: 3, or any of its sequence variants recited above as well as molecules comprising the antigen-binding portion of an antibody specific for said polypeptide and said polypeptide sequence variants as diagnostic marker/agent.

Claims 9 and 13-15 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 9 and 13-15 are partly drawn to an isolated polypeptide comprising **(A)** a protein having the sequence of SEQ ID NO: 4 or a protein encoded by a strand of full length cDNA having the sequence of **(B)** a naturally occurring polynucleotide comprising the sequence of SEQ ID NO: 3, and **(C)** a molecule which comprises the antigen-binding portion of an antibody specific for said isolated polypeptide. These embodiments are described.

However, the claims also embrace an isolated polypeptide comprising a protein encoded by **(a)** a naturally occurring polynucleotide having at least 70% identity with naturally occurring polynucleotide comprising SEQ ID NO: 3, **(b)** an isolated polypeptide comprising a protein encoded by a naturally occurring polynucleotide capable of hybridizing under moderately stringent conditions to a naturally-occurring polynucleotide of SEQ ID NO: 3 **(c)** or its 70%

homologue, **(d)** a variant of an isolated polypeptide having at least 70% identity to the protein encoded by the polynucleotide of **(a), (b),** and **(c)**, or a functional derivative or salt of **(a), (b), (c), and (d)**; or a molecule which comprises the antigen-binding portion of an antibody specific for said isolated polypeptide.

The specification discloses SEQ ID NO: 3 which corresponds to the DNA encoding the of protein of SEQ ID NO: 4. SEQ ID Numbers 3 and 4 meet the written description and enablement provisions of 35 USC 112, first paragraph.

With regard to embodiments (a) through (d) recited above, however, none of these sequences meet the written description provision of 35 USC 112, first paragraph. The specification provides insufficient written description to support the genus encompassed by the claim.

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention.* The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.)

With the exception of SEQ ID Numbers 3 and 4, the skilled artisan cannot envision the detailed chemical structure of the encompassed proteins, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. The nucleic acid itself is required. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993) and

Amgen Inc. V. Chugai Pharmacentical Co. Ltd., 18 USPQ2d 1016. In Fiddes v. Baird, 30 USPQ2d 1481, 1483, claims directed to mammalian FGF's were found unpatentable due to lack of written description for the broad class. The specification provided only the bovine sequence.

Finally, University of California v. Eli Lilly and Co., 43 USPQ2d 1398, 1404, 1405 held that:

> ...To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention." *Lockwood v. American Airlines, Inc.* , 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (1997); *In re Gosteli* , 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989) (" [T]he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed."). Thus, an applicant complies with the written description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." *Lockwood* , 107 F.3d at 1572, 41 USPQ2d at 1966.
>
> An adequate written description of a DNA, such as the cDNA of the recombinant plasmids and microorganisms of the '525 patent, "requires a precise definition, such as by structure, formula, chemical name, or physical properties," not a mere wish or plan for obtaining the claimed chemical invention. *Fiers v. Revel* , 984 F.2d 1164, 1171, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993). Accordingly, "an adequate written description of a DNA requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it; what is required is a description of the DNA itself." Id. at 1170, 25 USPQ2d at 1606.
>
> The name cDNA is not itself a written description of that DNA; it conveys no distinguishing information concerning its identity. While the example provides a process for obtaining human insulin-encoding cDNA, there is no further information in the patent pertaining to that cDNA's relevant structural or physical characteristics; in other words, it thus does not describe human insulin cDNA. Describing a method of preparing a cDNA or even describing the protein that the cDNA encodes, as the example does, does not necessarily describe the cDNA itself. No sequence information indicating which nucleotides constitute human cDNA appears in the patent, as appears for rat cDNA in Example 5 of the patent. Accordingly, the specification does not provide a written description of the invention of claim 5.

It is also noted that in Fiers v. Sugano (25 USPQ2d, 1601), the Fed. Cir. concluded that:

> "...if inventor is unable to envision detailed chemical structure of DNA sequence coding for specific protein, as well as method of obtaining it, then conception is not achieved until reduction to practice has occurred, that is, until after gene has been isolated...conception of any chemical substance, requires definition of that substance other than by its functional utility."

Therefore, only SEQ ID NO: 3 encoding the polypeptide of SEQ ID Number 4 and that which is encoded by polynucleotide of SEQ ID NO: 3, but not the full breadth of the claim (or none of the sequences encompassed by the claim) meets the written description provision of 35 USC 112, first paragraph. The species specifically disclosed are not representative of the genus because the genus is highly variant. Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 USC 112 is severable from its enablement provision. (See page 1115.)

Conclusion

No claims are allowed.

Inquiries

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Young J. Kim whose telephone number is (571) 272-0785. The Examiner can normally be reached from 8:30 a.m. to 6:00 p.m. Monday through Thursday. If attempts to reach the Examiner by telephone are unsuccessful, the Primary Examiner in charge of the prosecution, Dr. Kenneth Horlick, can be reached at (571) 272-0784. If the attempts to reach the above Examiners are unsuccessful, the Examiner's supervisor, Gary Benzion, can be reached at (571) 272-0782. Papers related to this application may be submitted to Art Unit 1637 by facsimile transmission. The faxing of such papers must conform with the notice published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 CFR 1.6(d)). NOTE: If applicant does submit a paper by FAX, the original copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED, so as to avoid the processing of duplicate papers in the Office. All official

documents must be sent to the Official Tech Center Fax number: (703) 872-9306. For Unofficial documents, faxes can be sent directly to the Examiner at (517) 273-0785. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (571) 272-0507.

Young J. Kim
Patent Examiner
Art Unit 1637
7/13/04

yjk

KENNETH R. HORLICK, PH.D
PRIMARY EXAMINER

7/19/04